REMARKS

Claim 1 has been amended to make explicit the presently claimed invention's requirement that the active ingredient *not* be complexed with cyclodextrin. Support for this amendment may be found in the specification (e.g., p.2:45-3:2). Claim 1 is further amended to make it more explicit that the polyethylene glycol included in the presently claimed process is one known to those of skill in the art to be used as a *binder* and not as a plasticizer. Support for this amendment may also be found in the specification (e.g., at p.3:39). The examiner rejects claims 1-9, and yet applicants are aware only of the six claims amended preliminarily. Claims 1-6 are presently at issue.

REJECTION UNDER 35 USC §103(A) OVER NAGAFUZI

Claims 1-6 are not obvious under 35 USC §103(a) over Nagafuzi et al. (US 5,290,569). To establish *prima facie* obviousness, the examiner must show in the prior art some suggestion or motivation to make the claimed invention, a reasonable expectation for success in doing so, and a teaching or suggestion of each claim element (*see, e.g., In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974)).

Nagafuzi discloses the formation of pharmaceutical composition granules through the combination of an active substance with a thermomelting binder, in the absence of solvent (col.1:40-42). The only mention of cyclodextrin in this reference is

in the examples, which employ a "[b]enexate hydrochloride/beta-cyclodextrin inclusion compound," referred to therein as "TA 903." This inclusion compound is an example of the "cyclodextrin-active ingredient complexes" discussed in the present specification, and one of the aims of the present invention is to provide a process for producing solid dosage forms without the need to produce such a cyclodextrin-active ingredient complex (p.2:43-p.3:2; cf. p.1:41-43).

Nagafuzi does not indicate that cyclodextrin may be employed to produce solid dosage forms in any manner other than as part of the disclosed cyclodextrin-active ingredient complex. In particular, the reference neither mentions nor suggests addition of cyclodextrin as a separate component, not complexed with the active ingredient. Without such a teaching or suggestion, one of skill in the art would not have the requisite motivation to modify the teaching of Nagafuzi, nor would such a person find a reasonable expectation for success of any kind in so doing. Accordingly, the process of the present claims is not *prima facie* obvious over the Nagafuzi reference.

Applicants respectfully request that the rejection of claims 1-6 over Nagafuzi et al. be withdrawn.

REJECTION UNDER 35 USC §103(A) OVER NAGAFUZI IN VIEW OF KLIMESH

Claims 1-6 are not obvious under 35 USC §103(a) over Nagafuzi et al. (US 5,290,569) in view of Klimesh et al. (US 4,880,585). To establish *prima facie* obviousness, the examiner must show in the prior art some suggestion or motivation to make the claimed invention, a reasonable expectation for success in doing so, and a

teaching or suggestion of each claim element (*see, e.g., In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974)).

As indicated above, Nagafuzi does not teach the process of the present invention, wherein an active ingredient *not* complexed with cyclodextrin is used to form a solid dosage form. Klimesh teaches a process for tableting extrudable pharmaceutical mixtures, and makes no mention of cyclodextrin. Accordingly, neither Klimesh nor Nagafuzi suggest the use of non-complexed active ingredients to make solid dosage forms, as presently claimed. As neither of these suggest this element, one of skill in the art would find neither motivation nor a reasonable expectation of success in modifying the combined disclosures of Nagafuzi and Klimesh to make the presently claimed invention. Accordingly, applicants respectfully request that the rejection of claims 1-6 under 35 USC §103(a) as obvious over Nagafuzi in view of Klimesh be withdrawn.

REJECTION UNDER 35 USC §103(A) OVER BAERT

Though no express statement of this rejection is given in the most recent office action, the examiner's response to arguments indicates that it has been maintained. However, as has been set forward earlier, claims 1-6 are not obvious over Baert et al. (WO 97/18839). To establish *prima facie* obviousness, the examiner must show in the prior art some suggestion or motivation to make the claimed invention, a reasonable

expectation for success in doing so, and a teaching or suggestion of each claim element (*see, e.g., In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974)).

Baert teaches a process for producing a solid mixture of one or more cyclodextrins, an active ingredient and, optionally, other additives, by melt-extrusion (p.5:24-26). Included within the enumerated optional additives are "pharmacologically acceptable plasticizers," among which "polyethylene glycols" are identified (p.6:1-3). As indicated in the attached encyclopedia excerpt, plasticizers are known in the art to be "organic liquids," and are used in addition to "binder components" (Ullmann's Encyclopedia of Industrial Chemistry, 5th (electronic) edition, *Paints and Coatings - Introduction*, §1.3.2.). As further illustrated in the Technical Information on Pluriol E®, only polyethylene glycols having a molecular weight less than 1000 are liquids, and therefore comply with this art-recognized definition of plasticizers. The polyethylene glycols described in Baert would, therefore, be interpreted by one of skill in the art to be liquid and to have molecular weights lower than 1000.

Review of the disclosure in Klimesh further indicates that one of skill in the art would not view polyethylene glycol binders to be the same as polyethylene glycols used as plasticizers. In that disclosure, a polymeric binder, which may be a polyethylene glycol, "should soften or melt" at the extrusion temperature (col.2:58,64-67). To reduce the glass transition temperature of the binder such that it does soften or melt at this

temperature, Klimesh discloses that plasticizers, including polyethylene glycols, may be used (col.3:1-6). A polyethylene glycol plasticizer used to reduce the glass transition temperature of a polyethylene glycol binder cannot logically be identical to that binder. One of skill in the art recognizes that polyethylene glycol binders and polyethylene glycol plasticizers are not identical.

Again, as indicated above, Baert discloses the combination and melt-extrusion of one or more cyclodextrins, an active ingredient, and optionally, a plasticizer. The polyethylene glycols for use as plasticizers would not be viewed by those of skill in the art to disclose or suggest polyethylene glycols used as binders. Accordingly, no motivation or reasonable expectation for success in substituting a polyethylene glycol binder for the polyethylene glycol plasticizer would be drawn therefrom by one of ordinary skill. The present claims are not *prima facie* obvious over Baert, and applicants respectfully request that the rejection of claims 1-6 under 35 USC §103(a) based on this reference be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, applicants consider that the rejections of record have been obviated and respectfully solicit passage of the application to issue.

Please charge any shortage in fees due in connection with the filing of this paper, including Extension of Time fees to Deposit Account No. 11-0345. Please credit any excess fees to such deposit account.

Respectfully submitted,
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DCL/kas

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

Please amend claim 1 to read as follows:

1. (twice amended) A process for producing solid dosage forms which are suitable for oral or rectal administration for humans and animals, wherein

a) 0.5 to 30% by weight of at least one active ingredient which is uncomplexed by cyclodextrin,

b) 0.5 to 70% by weight of at least one cyclodextrin,

c) 10 to 98% by weight of at least one polymeric binder, selected from the group consisting of polyethylene glycol having a molecular weight above 4000 [1000], polyvinylpyrrolidone, and copolymers comprising N-vinylpyrrolidone and vinyl acetate, and

d) 0 to 50% by weight of conventional excipients

are mixed and plasticized at a temperature below 220°C without adding a solvent and the resulting plastic mixture is shaped to produce the dosage form.

COPY OF ALL CLAIMS

1. (twice amended) A process for producing solid dosage forms which are suitable for oral or rectal administration for humans and animals, wherein

   a) 0.5 to 30% by weight of at least one active ingredient which is uncomplexed by cyclodextrin,

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   c) 10 to 98% by weight of at least one polymeric binder, selected from the group consisting of polyethylene glycol having a molecular weight above 4000, polyvinylpyrrolidone, and copolymers comprising N-vinylpyrrolidone and vinyl acetate, and

   d) 0 to 50% by weight of conventional excipients

   are mixed and plasticized at a temperature below 220°C without adding a solvent and the resulting plastic mixture is shaped to produce the dosage form.

2. A process as claimed in claim 1, wherein the molar ratio between active ingredient and cyclodextrin is in the range from 0.1 to 4.0.

3. A process as claimed in claim 1, wherein the plastic mixture is shaped in a molding calendar to produce the dosage forms.

4. A process as claimed in claim 3, wherein a molding calender with counterrotating molding rolls is used, with at least one of the molding rolls having on its surface depressions to receive and shape the plastic mixture.

5. A solid dosage form which is essentially free of aliphatic C_2-C_8-di- and -tricarboxylic acids and aromatic C_6-C_{10}-monocarboxylic acids, obtainable by a

process as claimed in claim 1.

6. A solid dosage form as claimed in claim 5, wherein at least 10% by weight of the active ingredient are present in the form of a cyclodextrin/active ingredient complex.

1.3.2. Plasticizers

Plasticizers (→ Plasticizers) are organic liquids of high viscosity and low volatility. The esters of dicarboxylic acids (e.g., dioctyl phthalate) are well-known examples. Plasticizers lower the softening and film-forming temperatures of the binders, They also improve flow, flexibility, and adhesion properties. Chemically, plasticizers are largely inert and do not react with the binder components. Most binders used today are inherently flexible and can be regarded as "internally plasticized" resins. For this reason, use of plasticizers has declined.